CHAPTER 5[†]

Synthesis of Non-natural Cyanthiwigin–Gagunin Hybrids

through Late-Stage Diversification of the Cyanthiwigin Natural Product Core

5.1 INTRODUCTION

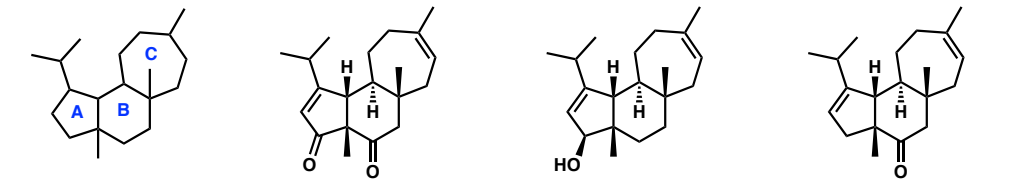
As described in Chapter 1, the derivatization of an easily accessible complex molecular scaffold offers many opportunities for synthetic and biological insight. Having probed the reactivity of the cyanthiwigin natural product core as a scaffold for the study of C–H functionalization, we sought to use the tricyclic framework as a starting point for accessing non-natural cyanthiwigin derivatives and assessing their biological activities. Taking our structural inspiration from the gagunin natural product family, we designed and executed the synthesis of several non-natural cyanthiwigin–gagunin "hybrid" molecules. The results of these investigations are described herein.

[†] The biological evaluations described in this chapter were performed in collaboration with Dr. Sangkil Nam and Dr. David Horne at the City of Hope.

5.1.1 THE CYANTHIWIGIN NATURAL PRODUCTS

Comprising a subset of a large class of bioactive natural products known as the cyathins, the cyanthiwigins are a family of diterpenoid natural products isolated from the marine sponges *Epipolasis reiswigi*[1] and *Myrmekioderma styx*.[2] Their complex architectures and interesting biological properties have attracted much attention in the chemical community. Of the 30 known cyanthiwigins, all except cyanthiwigin AC (**105**, Figure 5.2) possess 5–6–7 fused tricyclic carbon skeletons (**101**) featuring four contiguous stereocenters, two of which are quaternary. Additionally, many of these compounds display noteworthy biological activity against such disease agents as HIV-1 (cyanthiwigin B, **107**),[2] lung cancer and leukemia cells (cyanthiwigin C, **223**),[3] and primary tumor cells (cyanthiwigin F, **106**).[2]

*Figure 5.1 The cyathane skeleton (**101**) and biological properties of selected cyanthiwigins*

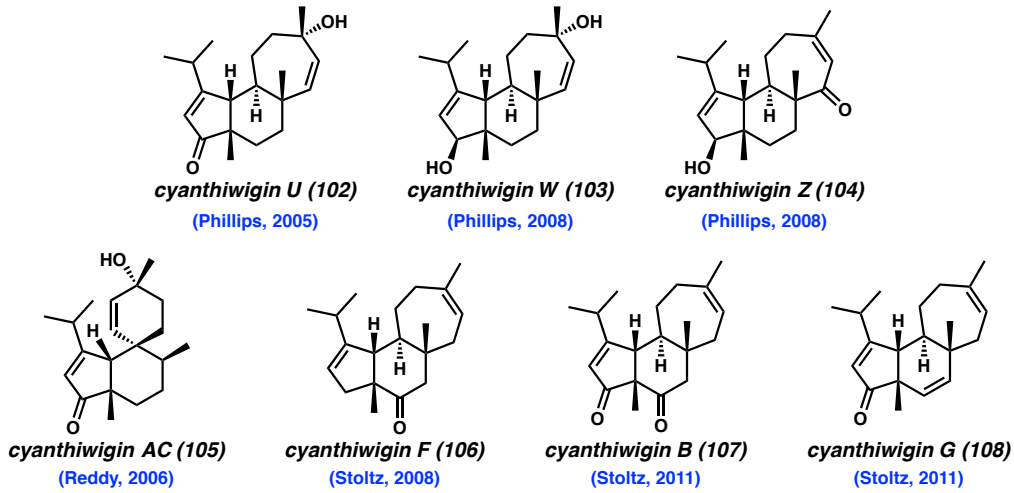


cyathane skeleton (101) ***cyanthiwigin B (107)*** anti-HIV ***cyanthiwigin C (223)*** anti-leukemia ***cyanthiwigin F (106)*** anti-tumor

Since not all of the cyanthiwigins have been isolated in large enough quantities for biological evaluation, exhaustive exploration of the medicinal properties of all 30 of the cyanthiwigins has remained elusive. Noting this along with the structural challenges presented by the molecules, chemists have targeted several members of the cyanthiwigin family for total synthesis efforts.[4] To date, seven cyanthiwigins have been prepared synthetically, including cyanthiwigins U (**102**),[5] W (**103**),[6] and Z (**104**)[6] by Phillips and

co-workers, cyanthiwigin AC (**105**) by Reddy and co-workers,[7] and cyanthiwigins F (**106**),[8] B (**107**),[9] and G (**108**)[9] by Stoltz and co-workers (Figure 5.2).

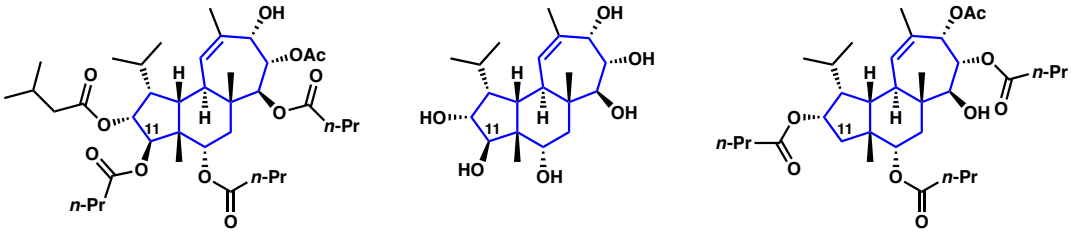
Figure 5.2 Cyanthiwigins prepared by total synthesis to date



5.1.2 THE GAGUNIN NATURAL PRODUCTS

Isolated from the sponge *Phorbas* sp. by Shin and co-workers off the coast of South Korea,[10] the gagunins are a family of diterpenoid natural products featuring the same 5–6–7 fused tricyclic core as the cyanthiwigins along with a range of biological activities. The main structural differences between the gagunins and the cyanthiwigins are the placement of the methyl substituent in the seven-membered C-ring and the degree of oxidation surrounding the carbocyclic framework. The density of functionalization and presence of numerous contiguous stereocenters (up to 11) make the gagunins challenging targets for total synthesis, and as such, only a partial synthesis of any gagunin has been completed to date.[11]

Figure 5.3 Structures and anti-leukemia activities of selected gagunins



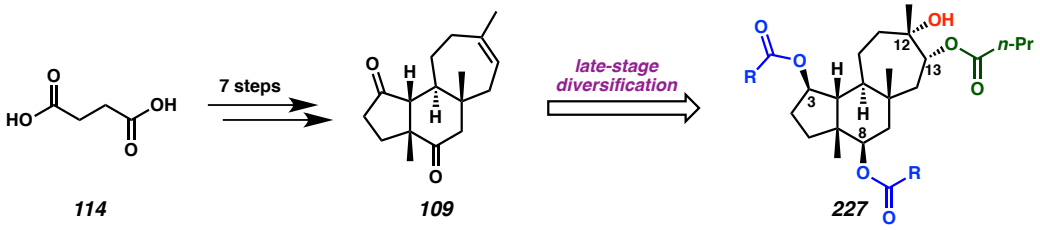
The gagunins exhibit cytotoxic activity against the human leukemia cell line K562, with gagunin E (**226**) displaying the most potent activity (LC_{50} = 0.03 μg/mL) out of all 17 known members of the natural product family.[10] Gagunin E (**226**) is over one thousand times more potent than the least biologically active member of the family, gagunin A (**224**) (Figure 5.3). Interestingly, these two compounds differ only in the placement and identity of the ester substituents surrounding the carbocyclic framework, an observation that led Shin and co-workers to propose that the biological properties of the gagunins are highly sensitive to the ester functionalities, especially at the C11 position. Indeed, evaluation of perhydroxylated gagunin A (**225**), in which all of the esters are hydrolyzed, revealed no appreciable biological activity, lending credence to Shin's hypothesis.

5.1.3 APPROACH TO HYBRID SYNTHESIS

With this in mind, we envisioned that the cyanthiwigin natural product core (**109**), for which we had previously established an efficient synthetic route,[8,9,12] could serve as a scaffold from which to access non-natural compounds combining structural features from both the cyanthiwigin and gagunin natural products (Scheme 5.1). Specifically, we

anticipated that the two carbonyl moieties and olefin in **109** could serve as functional handles for facile installation of ester functionalities, generating poly-esterified compounds (**227**) reminiscent of the densely oxygenated gagunins. Given the diverse biological activities displayed by the parent cyanthiwigins and gagunins, we hypothesized that some of these cyanthiwigin–gagunin "hybrid" molecules might exhibit interesting biological properties that could be correlated to structure through systematic fine-tuning of the ester functionalities. Overall, these efforts could enable the identification of exceptionally potent non-natural complex molecules[13] while providing insight into the reactivity of the cyanthiwigin core and the relationship between framework substitution and biological activity.

Scheme 5.1 Approach toward cyanthiwigin–gagunin hybrid synthesis



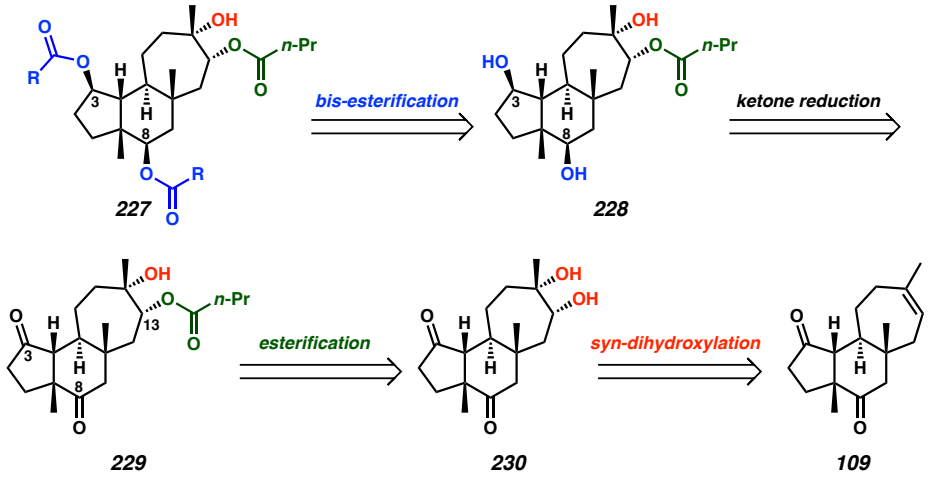
5.2 SYNTHESIS OF CYANTHIWIGIN–GAGUNIN HYBRIDS

At the outset of our efforts, we identified the C-ring olefin in **109** as a key starting point for diversification. Namely, oxygenation could be achieved through di-hydroxylation of the olefin with either *syn* or *anti* relative stereochemistry, ultimately giving rise to diastereomeric cyanthiwigin–gagunin hybrids.

5.2.1 SYN DIOL ROUTE

We began our studies targeting hybrid molecules derived from the *syn*-dihydroxylation pathway. Retrosynthetically, we envisioned that polyesterified hybrids **227** could arise through diversification of tris-hydroxylated compound **228**, which itself would be accessed through reduction of the A- and B-ring ketones in **229**. Mono-esterified compound **229** could be traced back to *syn*-diol **230**, which would result from *syn*-dihydroxylation of the cyanthiwigin core (**109**) (Scheme 5.2).

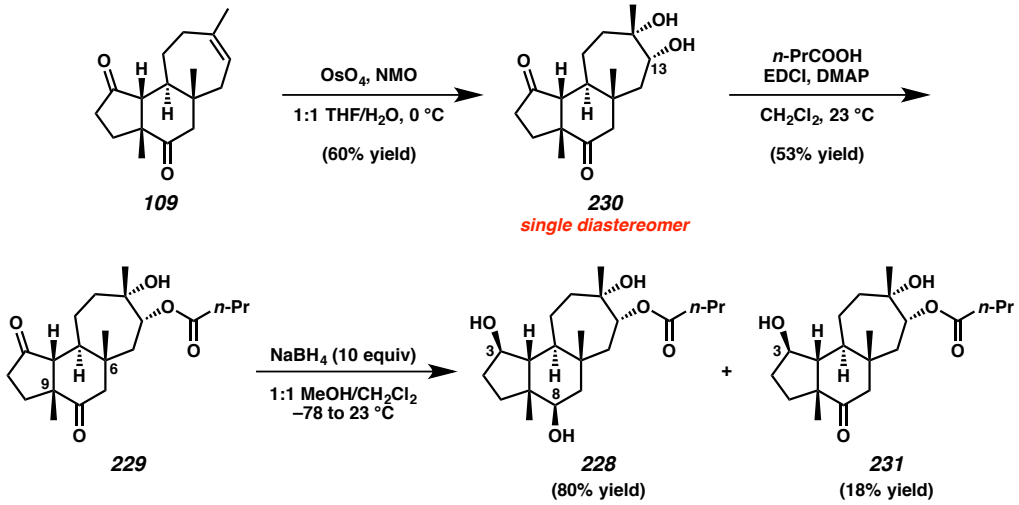
Scheme 5.2 Retrosynthetic analysis of cyanthiwigin–gagunin hybrid(s) ***227***



Preparation of the *syn*-diol-derived hybrids commenced with dihydroxylation of **109** using osmium tetroxide and NMO. We were pleased to find that *syn*-diol **230** was formed in good yield as a single diastereomer under these conditions. As observed in our previous studies on the hydrogenation and C–H functionalization of the cyanthiwigin core,[14] oxygenation occurred selectively from the α-face of the molecule, likely due to steric shielding of the β-face by the methyl substituent at the B–C ring juncture. Diol **230**

was subsequently treated with butyric acid, EDCI, and DMAP to effect selective esterification of the secondary C13 hydroxyl, furnishing tricyclic mono-ester **229** in moderate yield. Treatment of **229** with excess sodium borohydride resulted in the formation of triol **228** along with smaller quantities of mono-reduction product **231**, which were separable by column chromatography.

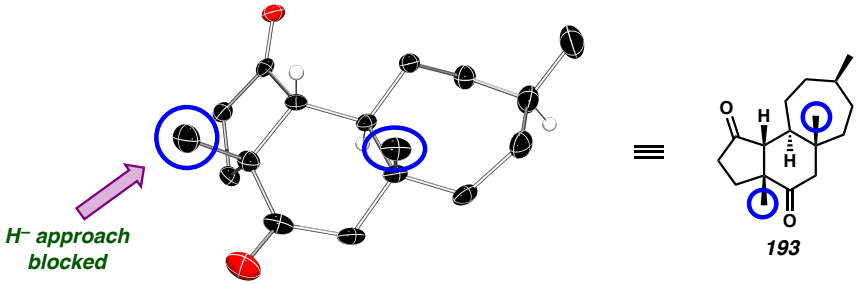
*Scheme 5.3 Preparation of key tris-hydroxylated intermediate **228** in the syn-diol route*



Notably, hydride reduction occurred selectively from the α-face of diketone **229**, presumably due to steric factors as in previous cases. The spatial relationship of the C9 and C6 methyl substituents to the C3 and C8 ketones in the cyanthiwigin core can be observed in an X-ray crystal structure of hydrogenated tricycle **193** (Figure 5.4). We propose that the C9 and C6 methyls are instrumental in controlling the facial selectivity of reduction. Specifically, the C9 methyl effectively blocks approach of the hydride from the Burgi–Dunitz angle[15] on the β-face, necessitating attack from the more accessible α-face despite the concavity of the three-dimensional architecture of **229**. Likewise,

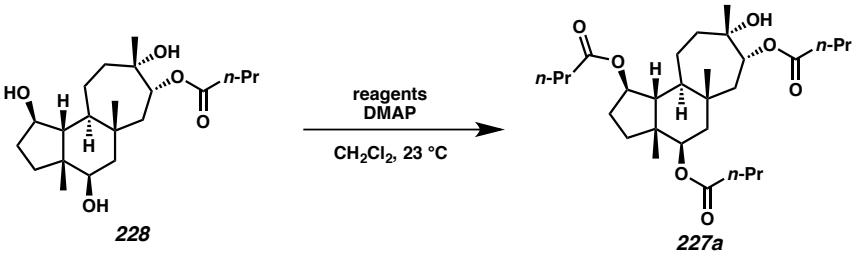
hydride approach toward the B-ring ketone from the β-face is rendered highly unfavorable by the C9 and C6 methyl substituents, giving rise to the observed stereochemistry at C3 and C8 in the product (**228**).

*Figure 5.4 Steric shielding of the β-face of the cyanthiwigin core caused by the C9 and C6 methyls, as illustrated by a crystal structure of hydrogenated tricycle **193***



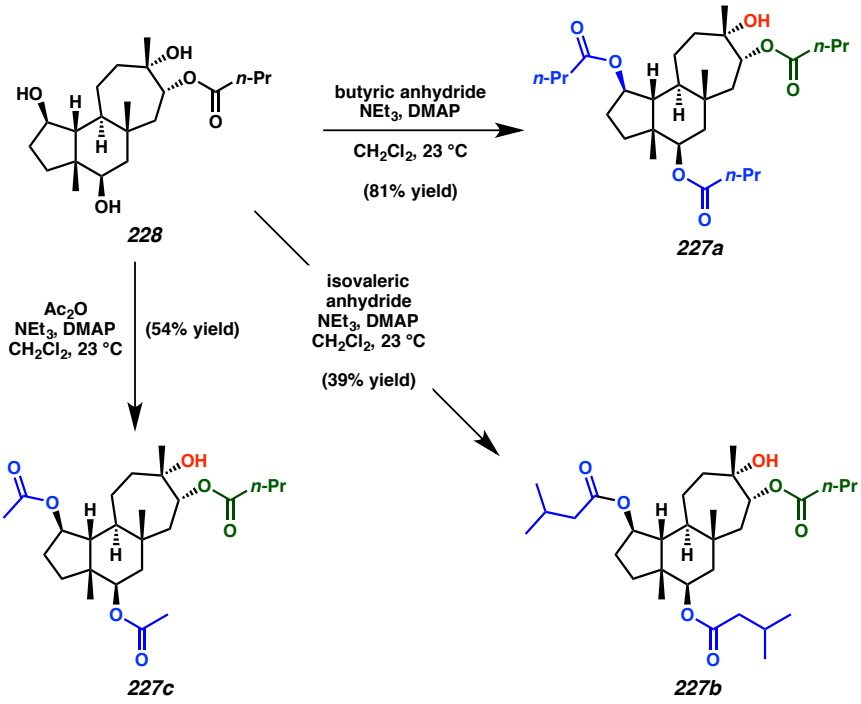
With tris-hydroxylated intermediate **228** in hand, we proceeded to the final transformation in generating cyanthiwigin–gagunin hybrids (**227**). Initial efforts at bis-esterification employing the same conditions used previously (butyric acid, EDCI, and DMAP) proved unsuccessful, returning large quantities of unreacted **228** (Table 5.1, Entry 1). Further attempts to access tri-ester **227a** using butyryl chloride and DMAP were also ineffective, instead converting **228** to a complex mixture of unidentified compounds (Entry 2). Finally, we discovered that the combination of butyric anhydride, triethylamine, and DMAP provided the optimal balance in reactivity, supplying cyanthiwigin–gagunin hybrid **227a** in high yield (Entry 3). Gratifyingly, application of these conditions to **228** using isovaleric anhydride or acetic anhydride enabled access to hybrids **227b** or **227c**, respectively (Scheme 5.4).

Table 5.1 Optimization of final esterification conditions for synthesis of hybrid ***227a***



Entry	Reagents	Result
1	*n*-PrCOOH, EDCI	low conversion
2	*n*-PrCOCl	messy mixture
3	$(n\text{-PrCO})_2O$, NEt_3	81% yield of ***227a***

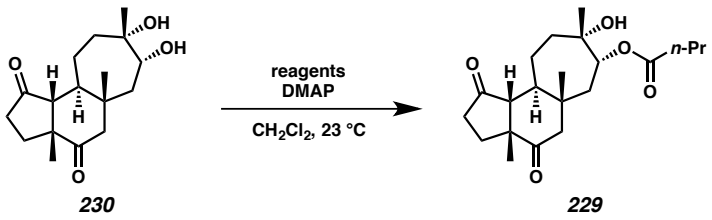
Scheme 5.4 Preparation of cyanthiwigin–gagunin hybrids ***227a–c*** *from common intermediate* ***228***



5.2.1.1 FURTHER SYNTHETIC CONSIDERATIONS

Having observed the discrepancies in efficacy between the three sets of esterification conditions employed in the preparation of **227a**, we re-examined the esterification of diol **230**. Comparison of the three different sets of conditions when applied to **230** revealed that, although the desired ester (**229**) was generated in serviceable quantities in every case, use of butyric anhydride and triethylamine in the presence of DMAP resulted in significantly higher yields (Table 5.2, Entry 3). As such, moving forward we planned to use anhydrides for esterification transformations whenever possible.

*Table 5.2 Comparison of different conditions for esterification of diol **230***



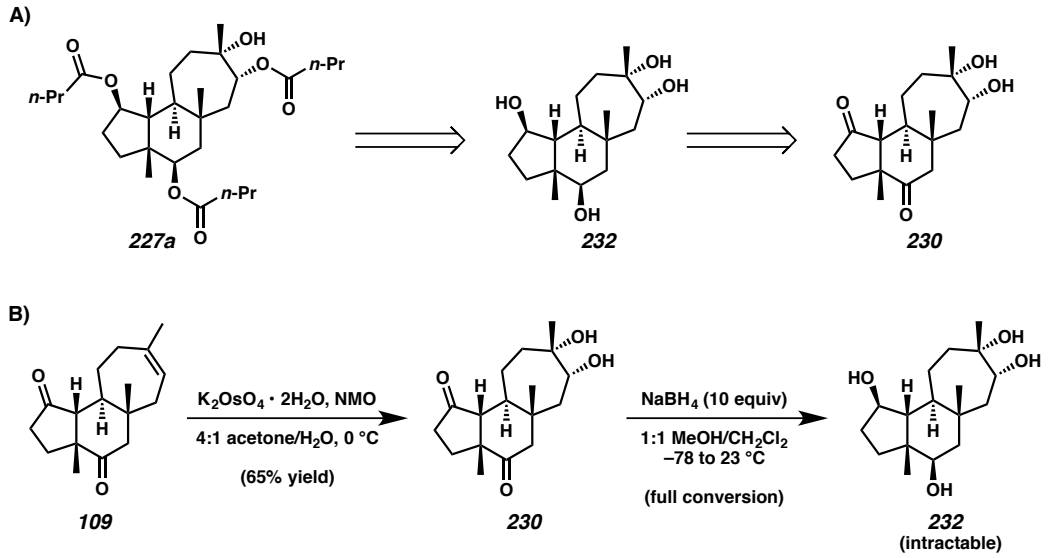
230 ***229***

Entry	Reagents	Yield
1	*n*-PrCOOH, EDCI	53%
2	*n*-PrCOCl	54%
3	$(n\text{-PrCO})_2O$, NEt_3	73%

For the preparation of cyanthiwigin–gagunin hybrid **227a**, we wondered if a global esterification strategy might be feasible through tetra-hydroxylated intermediate **232** (Scheme 5.5A). To investigate this possibility, we treated diol **230**, this time prepared through a catalytic dipotassium osmate dihydrate protocol, with excess sodium borohydride. Despite good conversion of starting material, the tetra-hydroxylated product **232** proved to be intractable, likely due to its high polarity and resistance to

extraction from the aqueous layer. As such, we determined that a global esterification strategy through a tetra-hydroxylated intermediate was not a viable approach for the preparation of cyanthiwigin–gagunin hybrids containing three identical ester substituents.

*Scheme 5.5 A) Alternate retrosynthesis for **227a** and B) attempted preparation of **232***

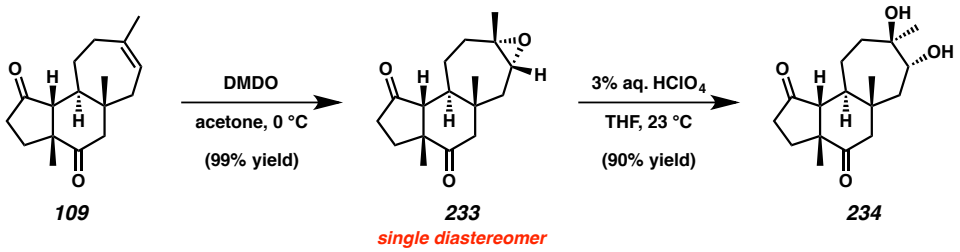


5.2.2 ANTI DIOL ROUTE

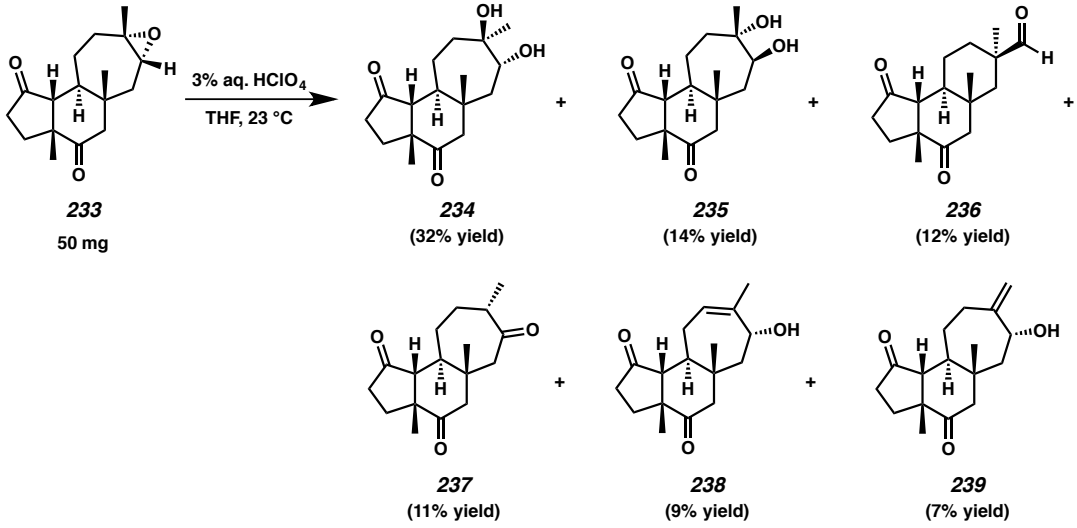
We next turned our attention to the preparation of cyanthiwigin–gagunin hybrids through the *anti*-diol route, which would enable access to compounds differing from the *syn*-diol route hybrids (**227**) at one stereocenter (C12). We reasoned that these molecules could be constructed in a similar fashion to **227**, except the route would begin with *anti*-diol instead of *syn*-diol formation. To this end, we treated tricycle **109** with dimethyldioxirane (DMDO) at 0 °C, forming epoxide **233** in excellent yield as a single diastereomer (Scheme 5.6). The high stereoselectivity of epoxidation resembles the

previously observed selectivity in the dihydroxylation of **109** (cf. Scheme 5.3), supporting our hypothesis that the β-face of the cyanthiwigin core is less accessible due to steric constraints. After unsuccessful attempts to open the epoxide under basic conditions (e.g., NaOH, $LiEt_3BH$), we found that treatment of epoxide **233** with catalytic perchloric acid delivered the desired *anti*-diol (**234**) in excellent yield.

*Scheme 5.6 Preparation of anti-diol **234** via acid-catalyzed epoxide-opening of **233***



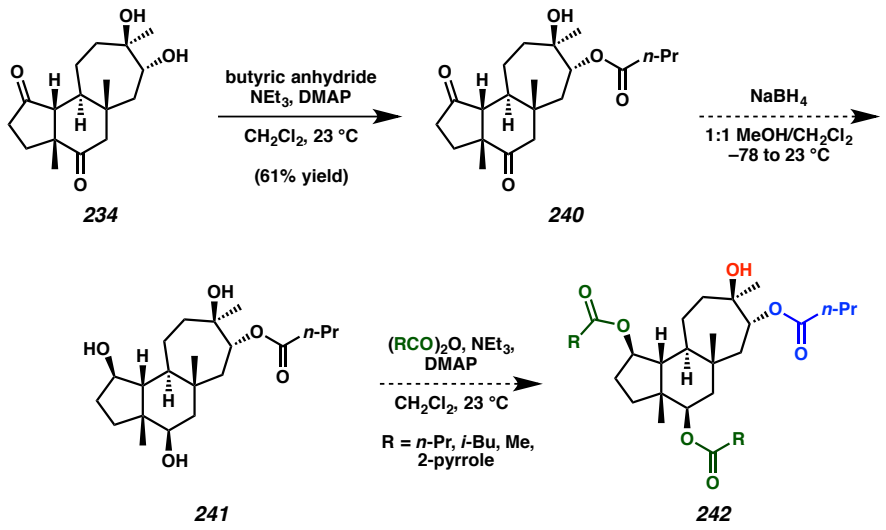
*Scheme 5.7 Formation of multiple products (**234–239**) from epoxide-opening of **233** (50 mg)*



Pleased with this result, we proceeded to repeat the sequence on a larger scale. While epoxidation of **109** consistently occurred in excellent yield, the acid-catalyzed epoxide-

opening of **233** proved to be less reliable. When 50 mg of epoxide **233** was subjected to conditions that had been effective on 5 mg, the formation of multiple products was observed. These compounds were isolated by column chromatography and characterized as compounds **234**–**239**. The desired *anti*-diol (**234**) comprised the major product at 32% yield while diastereomeric *anti*-diol **235** constituted the next most abundant product. Meinwald rearrangement[16] products **236** and **237** were formed in roughly equal amounts, and elimination products **238** and **239** were obtained in the smallest quantities.

*Scheme 5.8 Esterification of **234** and future efforts toward cyanthiwigin–gagunin hybrids **242***



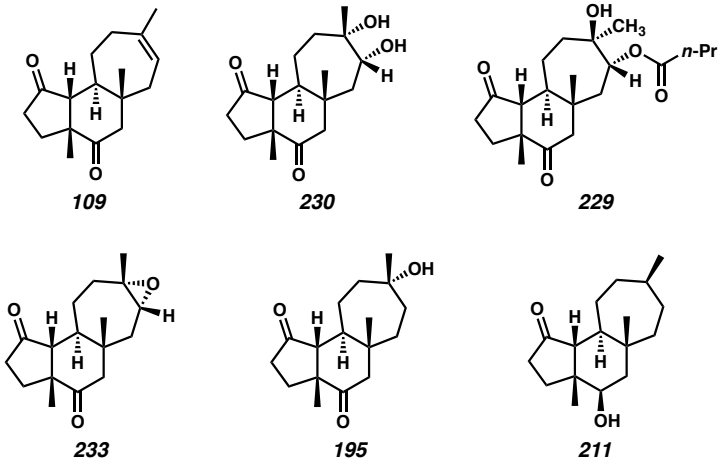
As evidenced by the low selectivity in the epoxide-opening reaction of **233**, further exploration will be required to identify a scalable procedure for the preparation of *anti*-diol **234**. A potential alternative to the two-step sequence outlined in Scheme 5.6 would be a Prévost reaction[17] on tricycle **109** to install the *anti*-diol directly. In the meantime, we have progressed diol **234** to mono-ester **240** using the previously optimized

esterification conditions. Future directions will entail the elaboration of **240** to cyanthiwigin–gagunin hybrids **242** (Scheme 5.8).

5.3 BIOLOGICAL STUDIES

While efforts are currently ongoing toward elucidating the biological properties of the cyanthiwigin–gagunin hybrid molecules, biological evaluation of synthetic intermediates has been initiated through collaboration with investigators at the City of Hope cancer research hospital. Preliminary results indicate that the compounds depicted in Figure 5.5 show no appreciable potency against melanoma cell line A2058 or prostate cancer cell line DU145. Further evaluation of these compounds and other intermediates in addition to the cyanthiwigin–gagunin hybrids (**227a**–**c**) against other cell lines and disease agents will be pursued through collaborations with other biological screening programs (e.g., National Cancer Institute, Eli Lilly and Co.).

Figure 5.5 Compounds sent to the City of Hope for biological testing to date



5.4 FUTURE DIRECTIONS

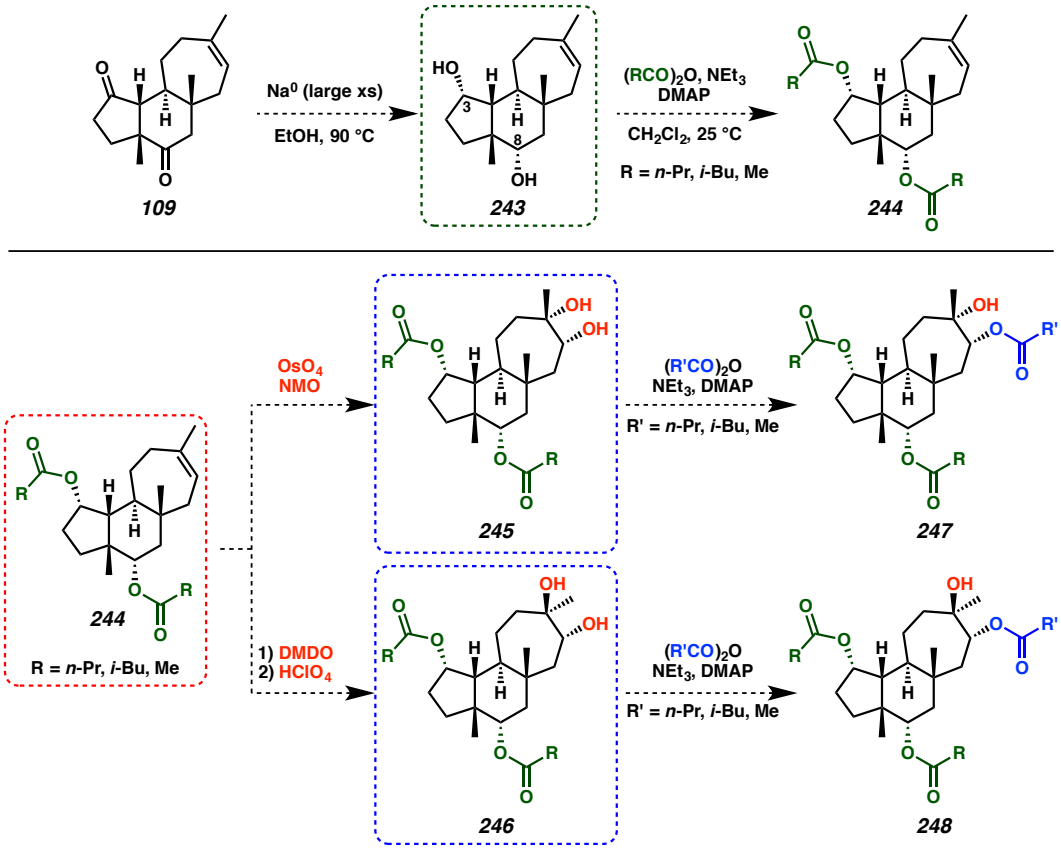
True to the nature of most late-stage diversification research programs, this project is quite open-ended with many avenues for cyanthiwigin–gagunin hybrid synthesis and biological evaluation yet to be explored. For each synthetic route to a hybrid molecule (e.g., *syn*-diol route, *anti*-diol route, etc.), there are nearly infinite combinations of ester functionalities that can be appended to the tricyclic core. Initial investigations have centered around butanoate, acetate, and isovalerate substituents based on their ubiquity among the natural gagunins, but as more insights into the activities of these compounds are generated, the ester functionalities can be re-designed as appropriate.

An alternative synthetic pathway that could be explored in future work involves the manipulation of stereochemistry at the C3 and C8 positions via carbonyl reduction. While SmI_2 and all hydride-based conditions examined (e.g., $NaBH_4$, L-selectride, K-selectride) have delivered exclusively α-face reduction products (i.e., **228**), preliminary results suggest that treatment of **109** with sodium metal in boiling ethanol effects rapid reduction of both carbonyls from the β-face, enabling access to diol **243** (Scheme 5.9), which features C3 and C8 stereochemistry opposite to what is generally observed with hydride reduction (cf. Scheme 5.3).

Notably, however, a drawback of this synthetic route is that carbonyl reduction would need to occur as the first step to avoid later reduction of ester carbonyl moieties under the strongly reducing conditions. Necessarily, this entails an earlier common intermediate for divergence (diol **243**, green box) and consequently a greater number of transformations to be performed in parallel afterwards, beginning with bis-esterification of **243** using various anhydrides (Scheme 5.9). The bis-esterified compounds (**244**)

would then serve as an additional bifurcation point (red box), as addition to the C-ring olefin could be effected through either a *syn* or *anti* pathway, as previously described. Finally, esterification of diols **245** and **246** (blue boxes) using a variety of anhydrides would furnish the hybrid molecules **247** and **248** (Scheme 5.9).

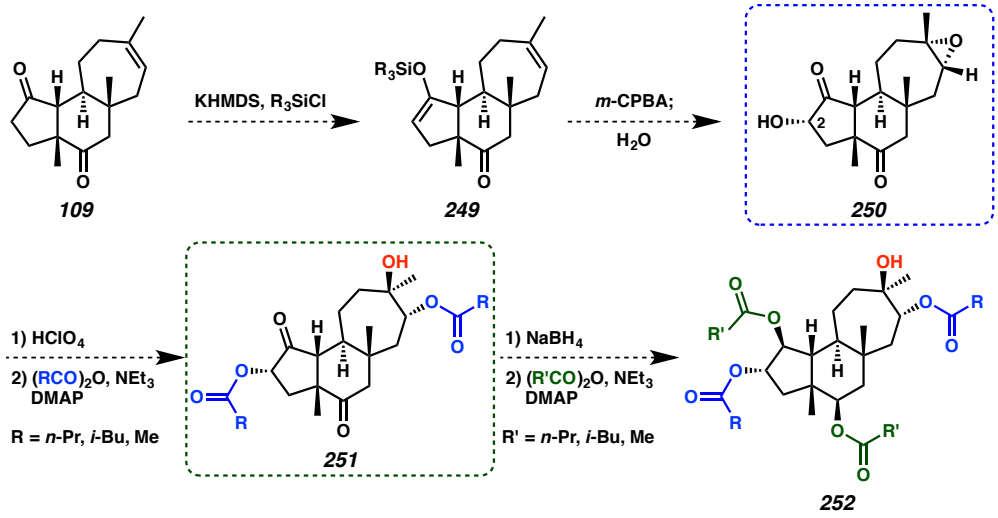
*Scheme 5.9 Future direction: preparation of hybrids **247** and **248** via β-face carbonyl reduction route, with boxes indicating points of divergence*



Another opportunity for further exploration involves the installation of an additional ester substituent on the carbocyclic core. Conversion of tricycle **109** to a silyl enol ether (**249**) and subsequent Rubottom oxidation with concurrent epoxidation of the C-ring olefin would afford C2-hydroxylated epoxide **250**, the first point of divergence in the

sequence (blue box, Scheme 5.10). Epoxide rupture followed by esterification using various anhydrides would yield bis-esterified compounds **251** (green box), which could be subjected to hydride reduction and esterfication with an array of anhydrides to generate the tetra-esterified hybrid molecules (**252**). Possessing an additional ester subsituent compared to the previously targeted hybrids (e.g., **227**, **242**, **247**, **248**), these highly oxygenated molecules would provide a unique perspective for biological study.

*Scheme 5.10 Future direction: preparation of hybrids **252** via Rubottom oxidation route*



5.5 CONCLUDING REMARKS

These investigations have revealed noteworthy patterns of reactivity in the complex tricyclic framework of the cyanthiwigin natural products. Findings from our studies into the reactivities of the C-ring olefin and the A- and B-ring carbonyls in **109** have enabled us to conclude that the β-face of the molecule is substantially less accessible than the α-face due to steric hindrance originating from the C9 and C6 methyl substituents. We

have prepared three cyanthiwigin–gagunin hybrid molecules (**227a–c**) using a common late-stage intermediate available in three steps from the cyanthiwigin natural product core. These compounds arose through a *syn*-dihydroxylation pathway, and we are currently applying this strategy to the preparation of hybrids from an *anti*-dihydroxylation pathway. Although initial biological studies have not indicated any appreciable cytotoxicity among several synthetic intermediates, evaluation of new compounds, including cyanthiwigin–gagunin hybrids and synthetic intermediates thereto, is underway.

In conclusion, a vast number of compounds are accessible through a multitude of synthetic pathways, including those yet to be examined. We anticipate that the synthetic insights derived from these exploratory studies will provide a strong foundation on which to expand in future efforts toward the synthesis and biological evaluation of non-natural cyanthiwigin–gagunin hybrid molecules.

5.6 EXPERIMENTAL SECTION

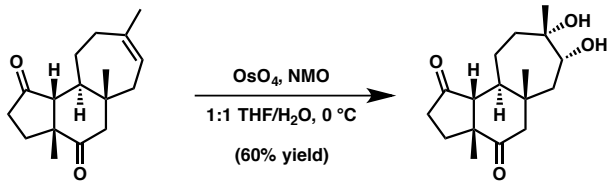
5.6.1 MATERIALS AND METHODS

Unless noted in the specific procedure, reactions were performed in flame-dried glassware under argon atmosphere. Dried and deoxygenated solvents (Fisher Scientific) were prepared by passage through columns of activated aluminum before use.[18] Methanol (Fisher Scientific) was distilled from magnesium methoxide immediately prior to use. Commercial reagents (Sigma Aldrich or Alfa Aesar) were used as received. Triethylamine (Oakwood Chemical) was distilled from calcium hydride immediately prior to use. Dimethyldioxirane (DMDO)[19] was prepared according to known procedures immediately prior to use. Brine is defined as a saturated aqueous solution of sodium chloride. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. NMR spectra were recorded on a Varian Mercury 300 spectrometer (at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR), a Varian Inova 500 spectrometer (at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR), or a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR), and are reported in terms of chemical shift relative to residual $CHCl_3$ (δ 7.26 and δ 77.16 ppm, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations

are used as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using thin film samples on KBr plates, and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer with fast atom bombardment (FAB+) ionization mode or were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+) mode. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using a 100 mm path-length cell.

5.6.2 PREPARATIVE PROCEDURES

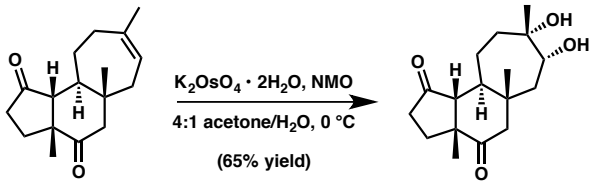
5.6.2.1 PREPARATION OF SYN-DIOL-DERIVED HYBRIDS



109 *230*
single diastereomer

Tricyclic Diol 230. To a solution of tricyclic diketone **109** (10 mg, 0.0384 mmol, 1.0 equiv) in 1:1 THF/H_2O (3.5 mL total volume) at 0 °C were added NMO (4 wt % solution in H_2O, 50 μL, 8.5 μmol, 0.22 equiv) and osmium tetroxide (50 wt % solution in H_2O, 0.1 mL, 0.410 mmol, 10.7 equiv). The resulting mixture was stirred at 0 °C for 4 hours, after which time TLC analysis showed full consumption of **109**. The reaction was quenched at 0 °C with saturated aq. $Na_2S_2O_3$ and stirred vigorously for 4 hours before

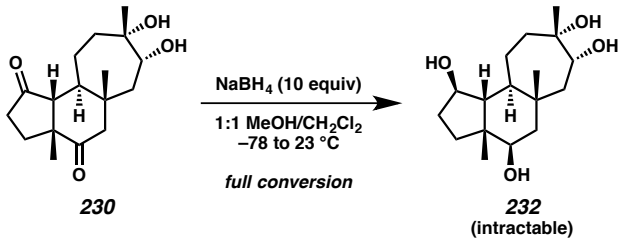
being diluted with dichloromethane (15 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (30% → 50% → 70% → 90% ethyl acetate in hexanes) to afford tricyclic diol **230** as a colorless oil (6.7 mg, 60% yield). R*f* = 0.10 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.62 (d, *J* = 10.1 Hz, 1H), 2.73 (d, *J* = 15.2 Hz, 1H), 2.50 (dd, *J* = 19.6, 10.2 Hz, 1H), 2.35 (dd, *J* = 19.6, 9.5 Hz, 1H), 2.29–2.23 (m, 1H), 2.14 (d, *J* = 16.2 Hz, 1H), 2.05–1.98 (m, 2H), 1.95 (d, *J* = 14.5 Hz, 1H), 1.86 (m, 1H), 1.79 (d, *J* = 11.3 Hz, 1H), 1.76–1.72 (m, 1H), 1.32 (d, *J* = 14.6 Hz, 1H), 1.28 (s, 3H), 1.12 (s, 3H), 1.06–0.98 (m, 1H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 218.2, 212.4, 74.2, 72.9, 61.2, 53.1, 51.0, 46.6, 45.5, 40.9, 40.1, 34.3, 31.0, 27.9, 21.8, 20.2, 19.3; IR (Neat Film, KBr) 3448 (br), 2961, 2934, 1735, 1702, 1466, 1384, 1176, 1125, 916, 731 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M–OH]^+$: 277.1804, found 277.1804; $[\alpha]^{25}_D$ –225.2 (*c* 1.00, $CHCl_3$).



109 ***230***

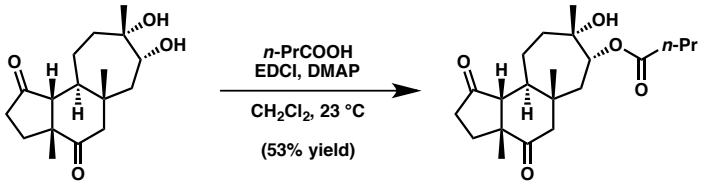
Dihydroxylation of 109 using Dipotassium Osmate Dihydrate. To a solution of tricyclic diketone **109** (50 mg, 0.192 mmol, 1.0 equiv) in 4:1 acetone/H_2O (10 mL total volume) at 0 °C were added NMO (45.0 mg, 0.384 mmol, 2.0 equiv) and dipotassium osmate dihydrate (7.1 mg, 0.0192 mmol, 0.1 equiv). The resulting mixture was stirred at

0 °C for 7 hours, after which time TLC analysis showed full consumption of **109**. The reaction was quenched with saturated aq. $Na_2S_2O_3$ at 0 °C and stirred vigorously for 30 minutes before being diluted with dichloromethane (15 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (50% → 75% → 100% ethyl acetate in hexanes) to afford tricyclic diol **230** as a colorless oil (36.8 mg, 65% yield).



230 ***232*** **(intractable)**

Sodium Borohydride Reduction of 230. To a solution of diol **230** (5.7 mg, 0.0194 mmol, 1.0 equiv) in 1:1 CH_2Cl_2/MeOH (2.0 mL total volume) was added a solution of sodium borohydride (7.3 mg, 0.194 mmol, 10.0 equiv) in 1:1 CH_2Cl_2/MeOH (0.5 mL total volume) at –78 °C. The reaction mixture was allowed to warm to 23 °C over the course of six hours. When TLC analysis indicated full consumption of starting material, the reaction was quenched with acetone (1.0 mL) and 2N NaOH (1.0 mL). The phases were separated, and the organic layer was immediately washed with brine (10 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the crude residue was subjected to silica gel column chromatography (100% ethyl acetate), but tetra-hydroxylated compound **232** was not obtained.

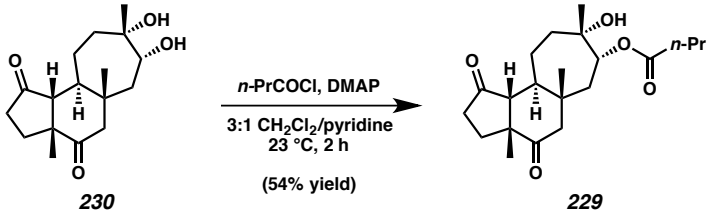


230
single diastereomer

229

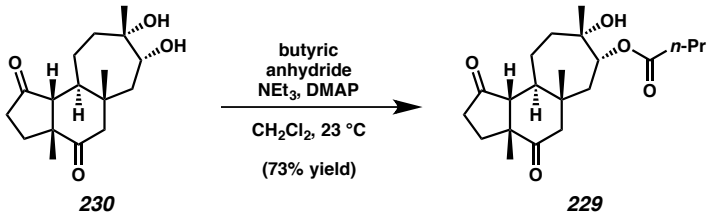
Tricyclic Monoester 229. To a solution of diol **230** (6.7 mg, 0.0228 mmol, 1.0 equiv) in dichloromethane (1.0 mL) at 23 °C were added EDCI (6.5 mg, 0.0342 mmol, 1.5 equiv), DMAP (2.8 mg, 0.0228 mmol, 1.0 equiv), and butyric acid (3.2 μL, 0.0342 mmol, 1.5 equiv). The resulting mixture was stirred at 23 °C for 24 hours, after which time the reaction was diluted with ethyl acetate (5 mL) and washed with 0.5 M HCl (3 mL), sat. aq. $NaHCO_3$ (3 mL), and brine (3 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated, and the crude residue was purified by silica gel column chromatography (15% → 25% → 35% → 55% ethyl acetate in hexanes) to afford monoester **229** as a colorless oil (4.4 mg, 53% yield). R*f* = 0.33 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.86 (d, *J* = 10.6 Hz, 1H), 2.55 (d, *J* = 15.1 Hz, 1H), 2.53–2.46 (m, 1H), 2.41–2.34 (m, 1H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.27–2.17 (m, 2H), 2.14 (d, *J* = 15.2 Hz, 1H), 2.07–2.01 (m, 1H), 2.01–1.95 (m, 1H), 1.88 (d, *J* = 12.6 Hz, 1H), 1.79–1.73 (m, 1H), 1.70–1.64 (m, 3H), 1.55 (m, 1H), 1.20 (s, 3H), 1.17 (d, *J* = 14.3 Hz, 1H), 1.14 (s, 3H), 1.13–1.07 (m, 1H), 0.94 (t, *J* = 7.4, 14.8 Hz, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 218.0, 211.8, 172.7, 74.6, 73.5, 61.1, 52.6, 50.9, 47.4, 43.3, 40.2, 40.0, 36.5, 34.3, 31.1, 28.6, 21.8, 20.2, 18.6, 18.0, 13.8 ; IR (Neat Film, KBr) 3503 (br), 2964, 2934, 2875, 1735, 1705, 1458, 1379, 1258, 1177, 988, 732 cm^{-1};

HRMS (FAB+) *m/z* calc'd for $C_{21}H_{31}O_4$ $[M–OH]^+$: 347.2222, found 347.2229; $[\alpha]^{25}_D$ – 277.4 (*c* 1.00, $CHCl_3$).



230 ***229***

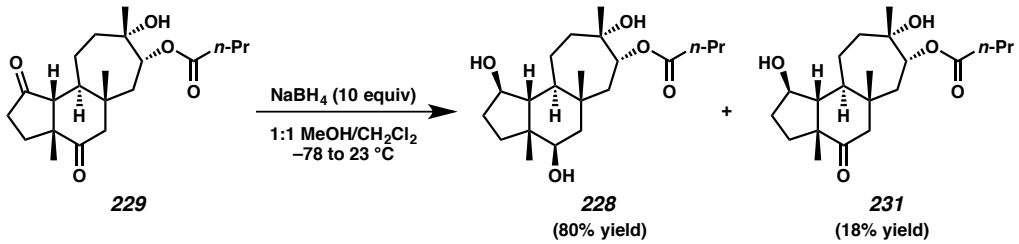
Esterification of 230 using Butyryl Chloride. To a solution of diol **230** (30.0 mg, 0.102 mmol, 1.0 equiv) in 3:1 CH_2Cl_2/pyridine (4.0 mL total volume) at 23 °C were added butyryl chloride (53 μL, 0.510 mmol, 5.0 equiv) and DMAP (12.5 mg, 0.102 mmol, 1.0 equiv). The resulting mixture was stirred at 23 °C for 2 hours, after which time the reaction was cooled to 0 °C and quenched with H_2O (5.0 mL) and saturated aq. NH_4Cl (5.0 mL), then extracted with ethyl acetate (2 x 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (15% → 30% → 45% ethyl acetate in hexanes) to afford monoester **229** as a colorless oil (20.2 mg, 54% yield).



230 ***229***

Esterification of 230 using Butyric Anhydride. To a solution of diol **230** (36.8 mg, 0.125 mmol, 1.0 equiv) in dichloromethane (6.5 mL) was added triethylamine (70 μL, 0.500 mmol, 4.0 equiv), butyric anhydride (60 μL, 0.375 mmol, 3.0 equiv), and DMAP

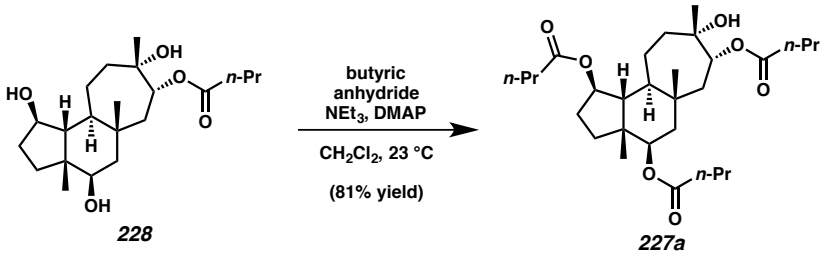
(7.6 mg, 0.0625 mmol, 0.5 equiv) at 23 °C. The resulting mixture was stirred for 1 hour, after which time TLC analysis indicated full consumption of **230**. The reaction was diluted with dichloromethane (10 mL) and washed with water (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (25% → 40% → 60% ethyl acetate in hexanes) to afford monoester **229** as a colorless oil (33.3 mg, 73% yield).



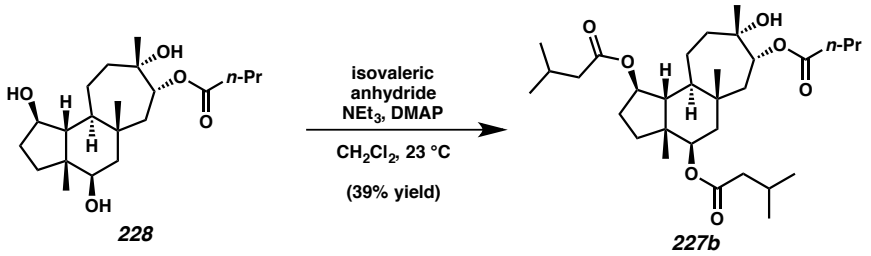
229 ***228*** (80% yield) ***231*** (18% yield)

Tris-hydroxylated Tricycle 228. To a solution of diketone **229** (31.0 mg, 0.0851 mmol, 1.0 equiv) in dichloromethane (2.0 mL) and methanol (2.0 mL) was added a solution of sodium borohydride (32.2 mg, 0.851 mmol, 10.0 equiv) in dichloromethane (1.0 mL) and methanol (1.0 mL) at –78 °C. The reaction mixture was allowed to warm to 23 °C over the course of 6 hours. When TLC analysis indicated full consumption of starting material, the reaction was quenched with acetone (2.0 mL) and 2N NaOH (2.0 mL). The phases were separated, and the organic layer was immediately washed with brine (10 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the crude residue was purified by silica gel column chromatography (15% ethyl acetate in hexanes), furnishing triol **228** (25.0 mg, 80% yield) and diol **231**

(5.6 mg, 18% yield). **Triol 228:** R*f* = 0.19 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.87 (dd, *J* = 11.1, 2.5 Hz, 1H), 4.01 (td, *J* = 6.2, 2.9 Hz, 1H), 3.69 (dd, *J* = 8.7, 5.8 Hz, 1H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.06–1.99 (m, 1H), 1.99–1.95 (m, 1H), 1.94–1.88 (m, 1H), 1.84–1.78 (m, 1H), 1.73–1.62 (m, 6H), 1.60 (m, 1H), 1.53–1.50 (m, 2H), 1.38–1.35 (m, 1H), 1.34–1.32 (m, 1H), 1.26–1.23 (m, 1H), 1.18 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.8, 80.5, 76.4, 74.2, 73.3, 57.6, 46.4, 45.9, 45.7, 45.1, 39.3, 37.5, 36.6, 35.0, 33.4, 29.6, 23.2, 22.5, 21.5, 18.7, 13.9; IR (Neat Film, KBr) 3402 (br), 2933, 2874, 1715, 1463, 1384, 1307, 1263, 1196, 1097, 1032, 916, 732 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{36}O_5K$ $[M+K]^+$: 407.2194, found 407.2196; $[\alpha]^{25}_D$ –20.7 (*c* 1.00, $CHCl_3$). **Diol 231:** R*f* = 0.25 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.90 (d, *J* = 10.7 Hz, 1H), 4.19 (t, *J* = 5.3, 2.1 Hz, 1H), 2.35–2.26 (m, 4H), 2.14–2.06 (m, 3H), 1.81–1.76 (m, 2H), 1.75–1.71 (m, 1H), 1.70–1.65 (m, 3H), 1.63–1.59 (m, 2H), 1.31 (s, 3H), 1.27–1.24 (m, 2H), 1.22 (s, 3H), 1.18–1.13 (m, 1H), 0.96 (t, *J* = 7.1, 14.8 Hz, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 214.7, 172.7, 80.5, 74.8, 73.7, 60.5, 53.7, 53.1, 52.5, 43.3, 40.7, 38.3, 36.9, 36.6, 34.5, 28.8, 23.9, 22.6, 18.6, 18.2, 13.8; IR (Neat Film, KBr) 3443 (br), 2964, 2934, 1731, 1694, 1463, 1384, 1264, 1190, 1140, 1030, 992, 920, 732 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{35}O_5$ $[M+H]^+$: 367.2484, found 367.2471; $[\alpha]^{25}_D$ –21.9 (*c* 1.21, $CHCl_3$).

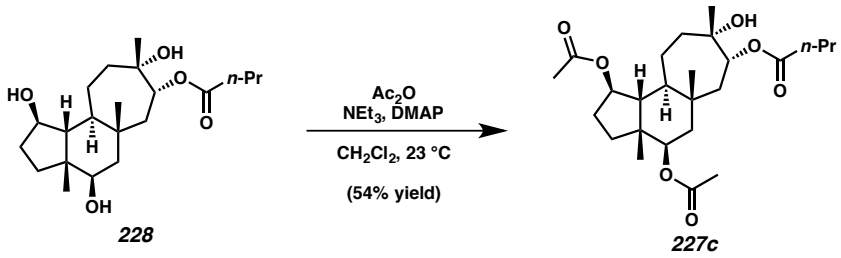


Cyanthiwigin–Gagunin Hybrid 227a. To a solution of tricyclic triol **228** (10.2 mg, 0.0277 mmol, 1.0 equiv) in dichloromethane (2.0 mL) was added triethylamine (30 μL, 0.222 mmol, 8.0 equiv), butyric anhydride (30 μL, 0.166 mmol, 6.0 equiv), and DMAP (3.4 mg, 0.0277 mmol, 1.0 equiv) at 23 °C. The resulting mixture was stirred for 2 hours, after which time TLC analysis indicated full consumption of **228**. The reaction was diluted with dichloromethane (5 mL) and washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (10% → 40% → 60% ethyl acetate in hexanes) to afford cyanthiwigin–gagunin hybrid **227a** as a colorless oil (11.4 mg, 81% yield). Rf = 0.16 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.10–5.06 (m, 1H), 4.95–4.89 (m, 2H), 2.32–2.29 (m, 2H), 2.28–2.23 (m, 4H), 2.01 (ddd, J = 14.9, 7.4, 3.1 Hz, 1H), 1.94 (dd, J = 13.9, 10.9 Hz, 1H), 1.88–1.82 (m, 1H), 1.74–1.69 (m, 2H), 1.69–1.61 (m, 8H), 1.59 (d, J = 4.3 Hz, 1H), 1.56–1.51 (m, 3H), 1.24 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 1.06–1.01 (m, 1H), 0.99–0.92 (m, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.2, 173.2, 172.8, 81.4, 75.7, 74.0, 73.9, 53.5, 46.8, 45.1, 44.4, 41.9, 40.6, 36.9, 36.8, 36.6, 36.1, 34.6, 29.5, 29.5, 23.7, 22.8, 19.2, 18.6, 18.6, 18.5, 13.9, 13.8 (x2); IR (Neat Film, KBr) 3506 (br), 2966, 2936, 2876, 1731, 1461, 1384, 1258, 1184, 1144, 1092, 981 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{29}H_{49}O_7$ $[M+H]^+$: 509.3478, found 509.3464; $[\alpha]^{25}_D$ –11.4 (*c* 1.14, $CHCl_3$).



Cyanthiwigin–Gagunin Hybrid 227b. To a solution of tricyclic triol **228** (5.4 mg, 0.0147 mmol, 1.0 equiv) in dichloromethane (1.0 mL) was added triethylamine (16 μL, 0.118 mmol, 8.0 equiv), isovaleric anhydride (17 μL, 0.0879 mmol, 6.0 equiv), and DMAP (1.8 mg, 0.0147 mmol, 1.0 equiv) at 23 °C. The resulting mixture was stirred for 1 hour, after which time TLC analysis indicated full consumption of **228**. The reaction was diluted with dichloromethane (5 mL) and washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (10% → 30% ethyl acetate in hexanes) to afford cyanthiwigin–gagunin **227b** as a colorless oil (3.1 mg, 39% yield): R*f* = 0.70 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.11–5.08 (m, 1H), 4.98–4.91 (m, 2H), 2.32 (t, *J* = 7.4, 14.8 Hz, 2H), 2.27–2.21 (m, 1H), 2.21 (s, 1H), 2.20–2.16 (m, 4H), 2.16–2.08 (dddd, *J* = 12.9, 9.5, 8.1, 6.3 Hz, 2H), 2.05–1.99 (m, 1H), 1.96 (dd, *J* = 14.0, 11.0 Hz, 1H), 1.85 (m, 1H), 1.83 (s, 1H), 1.74–1.71 (m, 1H), 1.71–1.67 (m, 2H), 1.66–1.60 (m, 2H), 1.57–1.52 (m, 2H), 1.31–1.28 (m, 1H), 1.28–1.23 (m, 2H), 1.21 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 1.00–0.95 (m, 15H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.8, 172.7, 172.7, 81.3, 75.7, 74.0, 73.9, 53.5, 46.6, 45.1, 44.4, 44.2, 44.0, 42.0, 40.5, 36.6, 36.2, 34.7, 29.6, 29.5, 25.9, 25.7, 23.8, 22.9, 22.7, 22.7, 22.6, 22.6, 19.3, 18.7, 13.9; IR (Neat Film, KBr) 3499 (br), 2961, 2874, 1731, 1466,

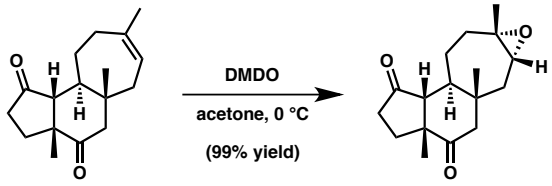
1384, 1294, 1257, 1189, 1120, 1095, 990 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{31}H_{51}O_6$ $[M–OH]^+$: 519.3686, found 519.3700; $[\alpha]^{25}_D$ –13.7 (*c* 0.31, $CHCl_3$).



Cyanthiwigin–Gagunin Hybrid 227c. To a solution of tricyclic triol **228** (7.0 mg, 0.0190 mmol, 1.0 equiv) in dichloromethane (2.0 mL) was added triethylamine (21 μL, 0.152 mmol, 8.0 equiv), acetic anhydride (11 μL, 0.114 mmol, 6.0 equiv), and DMAP (2.3 mg, 0.0190 mmol, 1.0 equiv) at 23 °C. The resulting mixture was stirred for 1 hour, after which time TLC analysis indicated full consumption of **228**. The reaction was diluted with dichloromethane (5 mL) and washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (20% → 40% ethyl acetate in hexanes) to afford cyanthiwigin–gagunin **227c** as a colorless oil (4.5 mg, 54% yield): R*f* = 0.56 (40% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08–5.05 (m, 1H), 4.93 (dd, *J* = 10.9, 1.8 Hz, 1H), 4.89 (t, *J* = 4.1 Hz, 1H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.26–2.17 (m, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02–1.98 (m, 1H), 1.94 (dd, *J* = 13.9, 10.9 Hz, 1H), 1.81 (s, 1H), 1.75–1.70 (m, 2H), 1.69–1.65 (m, 2H), 1.64–1.60 (m, 1H), 1.59–1.52 (m, 4H), 1.26–1.22 (m, 2H), 1.20 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.05 (ddd, *J* = 11.9, 9.7, 1.7 Hz, 1H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.8, 170.7, 170.6, 81.6, 75.7, 74.3, 74.0, 53.4, 46.8, 45.0, 44.4, 41.8, 40.6, 36.6, 36.1,

34.7, 29.5, 29.5, 23.6, 22.9, 21.6, 21.5, 19.2, 18.7, 13.9; IR (Neat Film, KBr) 3457 (br), 2966, 2934, 2877, 1732, 1463, 1384, 1245, 1184, 1145, 1022, 982, 908 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{41}O_7$ $[M+H]^+$: 453.2852, found 453.2835; $[\alpha]^{25}_D$ –12.3 (*c* 0.42, $CHCl_3$).

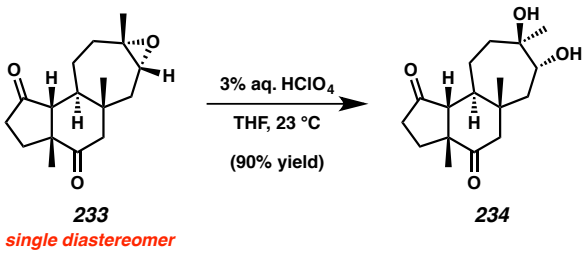
5.6.2.2 PREPARATION OF ANTI-DIOL-DERIVED INTERMEDIATES



109 ***233***
single diastereomer

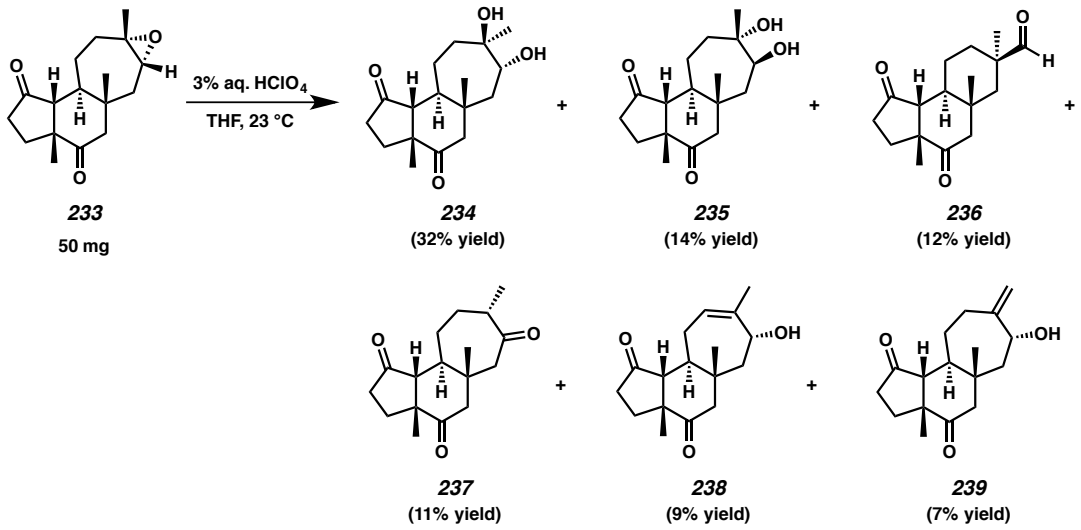
Epoxide 233. To a solution of tricyclic diketone **109** (50.0 mg, 0.192 mmol, 1.0 equiv) in acetone (2.0 mL) at 0 °C was added a solution of DMDO (0.0125M in acetone, 16.9 mL, 0.211 mmol, 1.1 equiv). The resulting mixture was stirred at 0 °C for 90 minutes, after which time the volatiles were removed under reduced pressure, affording epoxide **233** as a pale yellow oil (52.0 mg, 99% yield). This material was used without further purification. R*f* = 0.36 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.72 (t, *J* = 7.5, 14.4 Hz, 1H), 2.65 (d, *J* = 14.7 Hz, 1H), 2.52 (dddd, *J* = 19.5, 10.3, 2.0, 0.9 Hz, 1H), 2.37 (dddd, *J* = 19.4, 10.2, 9.1, 1.2 Hz, 1H), 2.30–2.22 (m, 1H), 2.12 (td, *J* = 7.3, 2.8 Hz, 1H), 2.07 (d, *J* = 14.8 Hz, 1H), 2.05–1.94 (m, 2H), 1.90 (d, *J* = 12.2 Hz, 1H), 1.80–1.73 (m, 1H), 1.66 (ddd, *J* = 12.3, 11.1, 2.8 Hz, 1H), 1.55–1.48 (m, 1H), 1.45–1.37 (m, 1H), 1.33 (s, 3H), 1.30–1.24 (m, 1H), 1.11 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.7, 211.9, 62.5, 60.3, 59.3, 52.2, 50.7, 47.4, 43.8, 41.8,

34.4, 34.3, 31.3, 23.9, 22.2, 21.7, 17.0; IR (Neat Film, KBr) 2958, 2932, 1736, 1705, 1466, 1383, 1171, 1007, 875, 735 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1798, found 277.1789; $[\alpha]^{25}_D$ –68.4 (*c* 0.12, $CHCl_3$).

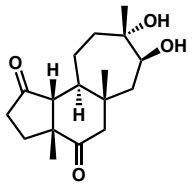


Anti Diol 234. To a solution of epoxide **233** (5.0 mg, 0.0181 mmol, 1.0 equiv) in THF (1.0 mL) at 23 °C was added perchloric acid (3 wt % solution in H_2O, 20 μL, 5.43 μmol, 0.3 equiv). The resulting mixture was stirred at 23 °C for 72 hours, after which time the reaction was diluted with ethyl acetate (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL), and brine (5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated, and the crude residue was purified by silica gel column chromatography (30% → 40% → 50% → 60% → 75% ethyl acetate in hexanes) to afford monoester **234** as a colorless oil (4.8 mg, 90% yield). R*f* = 0.10 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.88 (d, *J* = 10.1 Hz, 1H), 2.66 (d, *J* = 15.0 Hz, 1H), 2.53–2.44 (m, 1H), 2.41–2.33 (m, 1H), 2.27–2.21 (m, 1H), 2.16 (d, *J* = 15.0 Hz, 1H), 1.97–1.88 (m, 3H), 1.78–1.74 (m, 1H), 1.70–1.66 (m, 1H), 1.65 (m, 1H), 1.51 (m, 1H), 1.43 (m, 2H), 1.22 (s, 3H), 1.13 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.9, 212.2, 75.9, 74.1, 61.4, 52.9, 51.0, 46.5, 46.0, 41.8, 40.0, 34.3, 31.0, 24.5, 21.8, 19.9, 19.1; IR (Neat Film, KBr) 3444 (br), 2959, 2933, 1735, 1702, 1464, 1385, 1176, 1085,

992, 735 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{27}O_4$ $[M+H]^+$: 295.1909, found 295.1887; $[\alpha]^{25}_D$ –48.1 (*c* 1.62, $CHCl_3$).

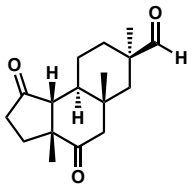


Epoxide-Opening Products 234–239. To a solution of epoxide **233** (47.2 mg, 0.171 mmol, 1.0 equiv) in THF (8.5 mL) at 23 °C was added perchloric acid (3 wt % solution in H_2O, 0.17 mL, 0.0512 mmol, 0.3 equiv). The resulting mixture was stirred at 23 °C for 72 hours, after which time the reaction was diluted with ethyl acetate (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL), and brine (10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated, and the crude residue was purified by silica gel column chromatography (30% → 50% → 60% → 75% → 100% ethyl acetate in hexanes) to afford diol **234** (16.3 mg, 32% yield) along with side products **235**–**239**. Yields and chacaterization data for **235**–**239** are listed below.



235

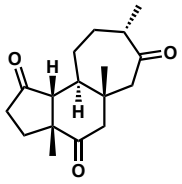
Diol 235: 7.2 mg, 14% yield. R*f* = 0.15 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (d, *J* = 10.3 Hz, 1H), 2.86 (d, *J* = 15.8 Hz, 1H), 2.60 (d, *J* = 6.7 Hz, 1H), 2.40–2.33 (m, 2H), 2.17 (d, *J* = 16.1 Hz, 1H), 2.08–2.04 (m, 1H), 1.96–1.91 (m, 2H), 1.86–1.83 (m, 1H), 1.73 (m, 1H), 1.60–1.54 (m, 1H), 1.51–1.46 (m, 2H), 1.29–1.27 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 221.7, 214.9, 75.8, 73.8, 60.1, 50.1, 49.0, 46.5, 44.9, 42.2, 39.8, 37.2, 32.4, 30.6, 24.8, 24.0, 21.5; IR (Neat Film, KBr) 3451 (br), 2958, 2932, 1737, 1704, 1455, 1384, 1268, 1169, 1147, 1087, 1070, 1036, 735 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{27}O_4$ $[M+H]^+$: 295.1909, found 295.1938; $[\alpha]^{25}_{D}$ –6.3 (*c* 0.72, $CHCl_3$).



236

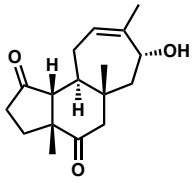
Aldehyde 236: 5.5 mg, 12% yield. R*f* = 0.65 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.49 (d, *J* = 1.5 Hz, 1H), 2.52–2.46 (m, 2H), 2.42–2.36 (m, 1H), 2.35–2.30 (m, 1H), 2.29–2.23 (m, 2H), 2.19 (d, *J* = 14.8 Hz, 1H), 1.97 (dd, *J* = 14.2, 2.4 Hz, 1H), 1.88–1.83 (m, 2H), 1.81–1.75 (m, 1H), 1.54 (m, 1H), 1.23–1.17 (m, 1H), 1.12 (s, 3H), 1.11–1.07 (m, 1H), 0.94 (s, 3H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.2, 211.5, 205.0, 61.0, 52.4, 51.3, 48.4, 45.9, 41.3, 39.0, 34.3, 31.8, 31.3, 25.0, 21.8,

21.8, 18.4; IR (Neat Film, KBr) 2957, 2931, 1738, 1704 (overlapping peaks), 1456, 1384, 1135, 839 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1819; $[\alpha]^{25}_D$ –41.5 (*c* 0.55, $CHCl_3$).



237

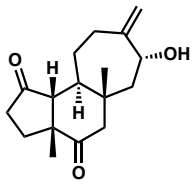
Triketone 237: 5.2 mg, 11% yield. R*f* = 0.50 (25% hexanes in ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.80 (d, *J* = 11.7 Hz, 1H), 2.74 (d, *J* = 15.0 Hz, 1H), 2.53 (dddd, *J* = 19.4, 10.3, 2.0, 0.8 Hz, 1H), 2.42 (m, 1H), 2.38–2.34 (m, 1H), 2.34–2.29 (m, 1H), 2.28–2.24 (m, 1H), 2.16–2.10 (m, 2H), 2.01–1.89 (m, 2H), 1.82–1.75 (m, 2H), 1.38–1.30 (m, 1H), 1.25–1.19 (m, 1H), 1.13 (s, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.6, 214.4, 211.4, 61.4, 54.2, 52.2, 50.9, 48.3, 46.5, 40.3, 34.3, 32.6, 31.2, 25.7, 21.7, 19.0, 18.6; IR (Neat Film, KBr) 2960, 2930, 1738, 1704 (overlapping peaks), 1456, 1384, 1222, 1176, 1053 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1814; $[\alpha]^{25}_D$ –5.4 (*c* 0.52, $CHCl_3$).



238

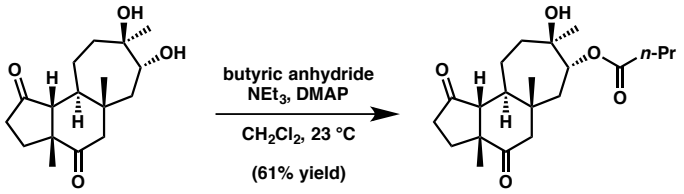
Allylic Alcohol 238: 4.3 mg, 9% yield. R*f* = 0.37 (25% hexanes in ethyl acetate); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.56–5.51 (m, 1H), 4.52 (d, *J* = 9.5 Hz, 1H), 2.93 (d, *J* = 14.9

Hz, 1H), 2.56–2.48 (m, 1H), 2.43–2.30 (m, 3H), 2.10 (d, *J* = 14.7 Hz, 1H), 1.97–1.90 (m, 2H), 1.87 (m, 1H), 1.77 (s, 3H), 1.75–1.69 (m, 2H), 1.58–1.54 (m, 1H), 1.11 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.2, 212.3, 143.1, 124.7, 69.6, 61.1, 52.9, 51.5, 49.1, 41.7, 41.6, 34.4, 31.1, 24.3, 21.7, 20.7, 19.6; IR (Neat Film, KBr) 3453 (br), 2960, 2923, 1737, 1704, 1462, 1384, 1164, 1124, 1051, 1002, 890, 735 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1796; $[\alpha]^{25}_D$ –46.1 (*c* 0.43, $CHCl_3$).



239

Allylic Alcohol 239: 3.4 mg, 7% yield. R*f* = 0.31 (25% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.05 (s, 1H), 4.97 (s, 1H), 4.31 (dd, *J* = 10.1, 5.5 Hz, 1H), 2.71 (d, *J* = 14.6 Hz, 1H), 2.60–2.49 (m, 1H), 2.43–2.22 (m, 5H), 2.09 (d, *J* = 14.6 Hz, 1H), 1.89–1.81 (m, 1H), 1.80–1.71 (m, 4H), 1.22 (m, 1H), 1.10 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.8, 212.3, 153.6, 113.6, 71.1, 62.6, 53.0, 50.9, 49.1, 45.1, 41.1, 34.4, 31.3 (x2), 28.9, 21.7, 17.3; IR (Neat Film, KBr) 3437 (br), 2928, 2871, 1732, 1704, 1455, 1384, 1262, 1165, 1019, 995, 905 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1803; $[\alpha]^{25}_D$ –47.6 (*c* 0.34, $CHCl_3$).



234 ***240***

Monoester 240. To a solution of diol **234** (13.0 mg, 0.0442 mmol, 1.0 equiv) in dichloromethane (4.0 mL) was added triethylamine (25 μL, 0.177 mmol, 4.0 equiv), butyric anhydride (22 μL, 0.132 mmol, 3.0 equiv), and DMAP (2.7 mg, 0.0221 mmol, 0.5 equiv) at 23 °C. The resulting mixture was stirred for 30 minutes, after which time TLC analysis indicated full consumption of **234**. The reaction was diluted with dichloromethane (5 mL) and washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (10% → 30% → 50% ethyl acetate in hexanes) to afford monoester **240** as a colorless oil (9.8 mg, 61% yield). R*f* = 0.30 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.99 (d, *J* = 10.7 Hz, 1H), 2.55 (d, *J* = 15.0 Hz, 1H), 2.52–2.44 (m, 1H), 2.41–2.34 (m, 1H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.21 (m, 1H), 2.13 (d, *J* = 15.1 Hz, 1H), 2.00–1.88 (m, 3H), 1.82–1.72 (m, 2H), 1.67 (q, *J* = 7.5 Hz, 2H), 1.61 (m, 1H), 1.50–1.37 (m, 3H), 1.14 (s, 3H), 1.14 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.7, 211.8, 174.4, 78.5, 75.1, 60.9, 52.7, 51.0, 47.2, 44.4, 41.6, 40.1, 36.6, 34.3, 31.1, 25.5, 21.8, 19.6, 18.6, 18.5, 13.8; IR (Neat Film, KBr) 3459 (br), 2963, 2933, 1732, 1705, 1463, 1456, 1380, 1260, 1177, 1086, 985 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{31}O_4$ $[M–OH]^+$: 347.2217, found 347.2218; $[\alpha]^{25}_D$ –44.4 (*c* 0.26, $CHCl_3$).

5.7 NOTES AND REFERENCES

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